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ORIGINAL RESEARCH

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Characterization of cerebral radiation necrosis following the treatment of sinonasal malignancies

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Abstract

Objectives: Our study aims to determine the incidence and potential risk factors for cerebral radiation necrosis (CRN) following treatment of sinonasal malignancies.

Methods: One hundred thirty-two patients diagnosed with sinonasal malignancies over an 18-year period were identified at two institutions. Forty-six patients meeting inclusion criteria and treated with radiation therapy were included for analysis. Demographic and clinical-pathologic characteristics were collected and reviewed. Post-treatment magnetic resonance imaging (MRI) at least 1 year following treatment was reviewed to determine presence or absence of CRN.

Results: CRN was identified on MRI in 8 of 46 patients (17.4%) following radiation treatment. Patients with a history of reirradiation were more likely to develop CRN (50% vs. 10.5%, $p < .05$). The BEDs of radiation were also higher in CRN patients compared to non-CRN patients, but this difference was not significant ($p > .05$). CRN patients had a higher proportion of tumors with skull base involvement than non-CRN patients (100% vs. 57.9%, $p = .037$). Demographics, comorbidities, pathology, primary tumor subsite, chemotherapy use, and stage of disease demonstrated no significant increase in risk of CRN.

Conclusions: Reirradiation and tumor skull base involvement were significant risk factors associated with CRN. Higher average total prescribed and BEDs of radiation were seen in the CRN groups, but these differences were not statistically significant. Gender, comorbidities, tumor subsite, tumor location, and treatment type were not significantly different between groups.

Level of evidence: Level 3.

KEYWORDS

cerebral radiation necrosis, nose and paranasal sinuses, radiation therapy, Sinonasal malignancies, sinus cancer

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1 | INTRODUCTION

Sinonasal malignancies are a rare subset of head and neck malignancies encompassing about 3% of all head and neck cancers.[1] Anterior skull base and sinonasal tumors may be treated with surgical resection, radiation therapy, chemotherapy or some combination of the three. Tumors with intracranial extension are more likely to receive multimodality treatment. Given the proximity of brain parenchyma to radiation therapy target volumes, it is often difficult, if not impossible, to completely exclude intracranial tissue from the radiation field despite advanced radiation delivery techniques.[2–5] Radiation therapy for head and neck malignancies, especially skull base and sinonasal tumors thus carries a potential risk of brain injury from radiation necrosis as a late toxicity.

Subsequent brain injury can come in a variety of forms but most severely as cerebral radiation necrosis (CRN) from late delayed radiation injury, which can occur anywhere from a few months to years after therapy.[2,5] CRN often mimics intracranial metastasis and is an irreversible process characterized by extensive vascular injury, demyelination, and white matter necrosis.[5] Presentation for CRN varies depending on location and extent and can range from a lack of symptoms and incidentally discovered on surveillance imaging to headaches, changes in consciousness, seizures, mass effect, or focal neurologic deficits.[2–5]

Radiation injury and CRN have been observed following radiation therapy for head and neck tumors.[3–5] Furthermore, it has been well documented that radiation therapy for nasopharyngeal carcinoma is capable of causing temporal lobe radionecrosis.[2,3,5] However, little literature exists characterizing CRN following radiation therapy for sinonasal malignancies. This study seeks to determine the risk factors and incidence of CRN in patients with sinonasal tumors treated with radiation therapy.

2 | MATERIALS AND METHODS

The Medstar Georgetown University Medical Center and Medstar Washington Hospital Center electronic medical record systems, tumor board databases, and radiation oncology databases were queried for patients evaluated between January 1, 2000, and December 31, 2018, that had ICD-9 or ICD-10 diagnoses consistent with sinonasal primary malignancies. Only patients with a history of a sinonasal malignancy treated with radiation therapy as a component of their care were included in the study. Patients who did not undergo radiation therapy for sinonasal malignancies or did not have available imaging were excluded. Because most cases of CRN have been reported in the literature to present around 1 year after treatment, patients with follow-up data of less than one year post-treatment were excluded to ensure sufficient clinical data and imaging to assess for CRN.[4,6] The Medstar Georgetown University Medical Center Institutional Review Board approved this study and waived informed consent under the protocol 483.

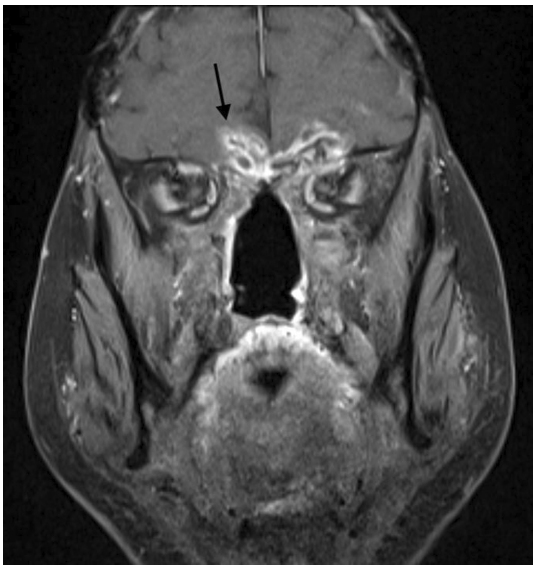

FIGURE 1 Post-radiation therapy T1-weighted post-contrast coronal magnetic resonance imaging of a patient with CRN. Image shows characteristic soap-bubble lesions (arrow) associated with CRN.

A retrospective chart review was conducted of patient medical records including provider notes, demographic information, imaging reports and studies, pathology, microbiology, and laboratory values. Records were reviewed for clinical–pathological characteristics including age, gender, ethnicity, comorbidities, cancer pathology and subsite, radiation history including modality and dosage, chemotherapy regimens, and presence and treatment of cancer recurrence. Cancer stage was determined using the American Joint Committee on Cancer 8th edition staging system. Patients were divided into early stage (TNM Stage I and II) and advanced stage (TNM Stage III and IV) malignancies.

Only patients with post-treatment MRIs at least one year following treatment available for review were included. Imaging was reviewed for each included patient with the assistance of a fellowship-trained neuroradiologist to determine if brain lesions were present. Using clinical information collected during chart review, these imaging changes were subclassified as tumor recurrence, CRN, or pseudoprogression. Diagnosis of CRN was made primarily based on post-treatment surveillance imaging. CRN lesions were identified by their characteristic "soap-bubble appearance," with hypointense nodular or curvilinear lesions on T1-weighted images, heterogeneous contrast enhancement on T1-weighted images, and hyperintense lesions on T2-weighted images (Figure 1). Initial pre-treatment MRIs were also examined to assess whether tumors had skull base involvement or whether a plane of normal tissue was present between the tumor and skull base.

For each prescribed radiation dose, fractionation (dose given per fraction) was used to calculate and compare the biologically effective dose (BED) of each radiation treatment to accurately compare doses

delivered with different fractionation schedules.[7] BED was calculated as a function of total dose, dose per fraction, linear dose damage response in tissue (α), and the quadratic dose response in tissue (β). This was performed assuming an α/β ratio of 3 Gy for late-responding normal brain tissue.

Categorial data was presented using frequencies and percentages and compared using Fisher's exact tests. Continuous variables, specifically radiation dosage, and the radiation BED were presented using medians and interquartile ranges and compared using Kruskal–Wallis *H*-tests. *p*-values of <.05 were used to determine significance.

3 | RESULTS

A total of 132 patients with sinonasal malignancies evaluated between January 1, 2000, and December 31, 2018, at Medstar Georgetown University Medical Center or Medstar Washington Hospital Center were identified. Forty-six patients met our inclusion criteria and had available imaging for review. Of the included patients, eight patients (17.4%) were found to have CRN on imaging review, and 38 patients (82.6%) did not have CRN (Table 1). The most common sinonasal tumor pathologies in our cohort were adenoid cystic carcinoma, squamous cell carcinoma, and melanoma.

Of the 46 patients that met inclusion criteria, 50% of patients found to have CRN were male, while 57% of patients without CRN were male. There were no significant differences in ethnicity or smoking history between CRN and non-CRN patients. Rates of comorbidities examined, which included diabetes mellitus, hypertension, heart disease, peripheral vascular disease, lung disease, obesity, and HIV, were also not significantly different between the two groups (Table 2).

Patients with CRN were diagnosed with CRN on average 4.69 years following their initial radiation treatment, but time of diagnosis ranged from 1.08 to 13 years post-treatment. One-quarter of CRN patients were asymptomatic. The other three-quarters of CRN patients had non-specific symptoms including headaches, worsening memory, difficulty sleeping, or seizures. When we stratified patients by tumor involvement of the skull base, all patients that developed CRN had tumors with skull base involvement, which was significantly greater than the 58% of patients without CRN that had tumors with skull base involvement (100% vs. 57.9%, $p = .037$). Patients without CRN were more likely to have sinonasal malignancies within the nasal cavity (68.4% vs. 12.5%, $p = .006$), but there were no other significant differences in development of CRN when stratifying by sinonasal malignancy subsites. When examining TNM staging, 87.5% of CRN patients were diagnosed at advanced stages compared to 72.7% of non-CRN patients. However, this difference was not statistically significant.

TABLE 2 Patient cohort demographics.

	CRN (8)	Non CRN (38)	*p*
Gender (%)			.713
Male	4 (50.0)	22 (57.9)	
Female	4 (50.0)	16 (42.1)	
Ethnicity (%)			1.000
Caucasian	5 (62.5)	20 (54.1)	
African American	2 (25.0)	12 (32.4)	
Other	1 (12.5)	5 (13.5)	
Smoker (%)	0 (0.0)	2 (5.3)	1.000
Diabetes mellitus	1 (12.5)	5 (13.2)	1.000
Hypertension	3 (37.5)	19 (50.0)	.702
Heart disease	0 (0.0)	8 (21.1)	.317
Peripheral vascular disease	1 (12.5)	4 (10.5)	1.000
Lung disease	0 (0.0)	1 (2.6)	1.000
Obesity (%)	2 (25.0)	7 (18.4)	.645
HIV (%)	0 (0.0)	1 (2.6)	1.000

TABLE 1 Patients with CRN.

Patient	Tumor type	Tumor location	Stage	Reirradiation	Symptoms
1	Sinonasal Undifferentiated Carcinoma	Left ethmoid cavity	T4N0M0	No	Asymptomatic
2	Adenoid cystic carcinoma	Right maxillary sinus	T4N0M0	Yes	Difficulty sleeping
3	Adenoid cystic carcinoma	Right maxillary sinus, Right ethmoid sinus	T4N0M0	No	Seizures
4	Plasmacytoma	Left sphenoid sinus	Stage I	No	Memory problems, dizziness, blurry vision, imbalance, seizure
5	Embryonal rhabdomyosarcoma	Left maxillary sinus	T2bN0M0	Yes	Headache
6	Esthesioneuroblastoma	Left nasal cavity	Kadish D	Yes	Lethargy, seizures
7	Adenoid cystic carcinoma	Right maxillary sinus	T4N0M0	No	Asymptomatic
8	Nasopharyngeal carcinoma[a]	Left nasal cavity	T1N2bM0	Yes	Tearing, nasal crusting

[a]Included for sinonasal recurrence.

TABLE 3 Radiation treatment and treatment modalities.

	CRN (8)	Non-CRN (38)	*p*-Value
Tumor stage (%)			
Early	1 (12.5)	9 (27.3)	.653
Advanced	7 (87.5)	24 (72.7)	
Radiation BED (cGy) (median [IQR])	11939.5 [11735.0, 14735.3]	10656.0 [10113.3, 11940.0]	.514
Radiation gross (cGy) (median [IQR])	6996.0 [4374.0, 7449.0]	6660.0 [5805.0, 6999.0]	.606
Re-irradiation (%)	4 (50.0)	4 (10.5)	.022
IMRT (%)	4 (50.0)	30 (78.9)	.178
Cyber knife (%)	5 (62.5)	14 (36.8)	.246
Chemotherapy	5 (71.4)	18 (47.4)	.414
Upfront surgery	4 (57.1)	24 (63.2)	1.000

A statistically significant larger proportion of patients that developed CRN had a history of reirradiation at 50% compared to non-CRN patients at 10.5% ($p = .022$) (Table 3). The median biologically effective dosage (BED) of radiation in CRN patients was also higher at 11940 cGy compared to non-CRN patients at 10656 cGy, but this difference was not significant. A larger proportion of CRN patients compared to non-CRN patients underwent CyberKnife radiation therapy rather than conventionally fractionated intensity modulated radiation therapy (IMRT), but this was not statistically significant (62.5% vs. 36.8%, $p = .246$). One of the patients in the CRN cohort was treated with proton therapy while two patients in the non-CRN cohort were treated with proton therapy, but this was not statistically significant (12.5% vs. 5.3%, $p = .444$). There were no significant differences between groups when stratifying based on upfront surgery or concurrent or sequential adjuvant chemotherapy.

4 | DISCUSSION

Sinonasal malignancies are rare, accounting for less than 1% of all malignancies and 3% of head and neck malignancies.[1] CRN as a result of radiation treatment for sinonasal malignancies is an even rarer occurrence, making CRN difficult to study and characterize.

Radiation remains a mainstay of treatment for sinonasal malignancies along with surgery, but it is not without risk. CRN is a late complication following radiation therapy and can occur anywhere from 6 months to decades after therapy.[3,6,8–10] Ahmad 2016 found that most cases of CRN presented around 1 year after treatment, while other literature has reported that 80% of cases occur within 3 years.[4,6] Incidence has been reported to be between 1% and 24% and varies considerably depending on radiation dosage and fractionation.[6,11] The high heterogeneity in CRN incidence, latency, and presentation highlights the difficulty in diagnosis and study of CRN.

Diagnosis of CRN remains a diagnostic challenge as it is difficult to discern whether brain lesions are consistent with pseudoprogression, tumor progression or recurrence, or CRN. Radiologically, pseudoprogression, tumor, and CRN have similar appearances, identifiable by new or enlarging lesions within the radiation field, enhancement with contrast, and edema; they can be differentiated by timing and progression on post-treatment surveillance imaging.

Pseudoprogression occurs in the subacute phase, usually less than 12 weeks following radiation treatment, and is characterized by increased contrast enhancement on T1-weighted MRI images as a result of increased vascular permeability from cytotoxic therapies such as radiation or chemotherapy.[6,12] Although confirmatory biopsy is necessary to exclude recurrence, intracranial biopsy is typically not performed due to its invasive nature unless suspicion for tumor is high. Instead, pseudoprogression is typically diagnosed retrospectively as the enhancing lesion improves or stabilizes without further invention.[6,12] Neurological symptoms may also be used to aid diagnosis as patients with pseudoprogression are less likely to experience neurological deterioration.[13]

In contrast to pseudoprogression, CRN is a delayed reaction to treatment usually seen 6 months to several years following radiation treatment. Radiation necrosis occurs most commonly at dosimetric "hot spots" and is characterized by necrosis, demyelination, and hemorrhage.[12,14] On MR imaging, CRN presents as an enhancing mass with a central area of necrosis, exhibiting a "soap-bubble" or "Swiss cheese-like" appearance.[14] On T2-weighted images, the solid portion of the necrotic mass is hypointense while the central necrotic component is hyperintense.[14] Tumor recurrence and CRN may be difficult to distinguish on imaging at an early stage, but at later stages, tumors tend to progress while CRN tends to remain stable, shrink, or disappear.[15]

Clinical features of CRN depend on the location and extent of lesions, so symptoms can vary widely from asymptomatic to significant neurological dysfunction. In patients treated with stereotactic radiosurgery for brain metastases, patients were reportedly symptomatic in 8–10%.[16] The heterogeneity and lack of specificity of presenting symptoms makes clinical diagnosis of CRN difficult. Nearly 75% of our CRN patients had varied symptoms including lethargy, headache, seizures, and worsening memory, but it is unclear what percentage of these can be specifically attributed to CRN. Treatment of CRN is also mixed; surgical resection of necrotic lesions has been reported, but medical therapy with corticosteroids has been recommended more often in recent literature.[3,4,9] The majority of CRN patients in in our cohort were initially managed conservatively with steroids or observation. Half of the CRN cohort eventually underwent resection of the area of radiation necrosis.

As one of the largest single-institution investigations of CRN following radiation treatment for sinonasal malignancies, we aimed to characterize CRN and identify risk factors that may lead to its development. Unlike previously published literature, our cohort includes both patients treated with high dose per fraction stereotactic body radiation therapy (SBRT) (1–5 fractions over the course of 1–2 weeks) and those who received conventionally fractionated daily radiation treatments over the course of 6–8 weeks. Overall, about 17% of our cohort of patients with sinonasal malignancies treated with radiation ultimately developed CRN, which is consistent with previously published literature.[6] More significantly, 50% of patients that underwent reirradiation developed CRN while only 10% of patients treated with a single radiation regimen developed CRN.

Previous literature reports that 60 Gy delivered in 1.8–2.0 Gy fractions is the upper limit of a "safe dose" of irradiation to the brain; as this limit is exceeded, incidence of CRN increases.[17] Lee et al.[18] examined temporal lobe necrosis following radiation for nasopharyngeal carcinoma and estimated that a 64 Gy at fractional dose of 2 Gy daily would result in a necrosis rate of 5% after 10 years. They concluded that fractionation, as calculated by a BED, was the most significant factor affecting cerebral necrosis.[18] Calculation of BEDs of each radiation treatment allows for accurate comparisons of doses delivered with different fractionation schedules.[7] The BED expresses the quantitative biological effect of radiation treatment (log cell kill) taking into account dose per fraction.

In our study, patients with CRN had higher gross total prescribed radiation dosages as well as higher BEDs than patients without CRN. However, these differences were not statistically significant. Our groups of patients with CRN and those without CRN received average gross total radiation doses of 70 Gy and 67 Gy for their sinonasal malignancies. Radiation injury to the brain itself as a result of radiation to the nasal cavity and sinuses would likely depend on proximity of the lesion to the skull base and areas included within the radiation field, and our data showing that all patients with CRN had tumors with skull base involvement while just over half of patients without CRN had tumors with skull base involvement supports this theory.

While BEDs were not significantly different between the two groups, we did find that presence of reirradiation was a significant risk factor associated with the development of CRN. Fan et al.[19] reported that reirradiation for nasal cavity and paranasal sinus cancers resulted in earlier and higher rates of brain necrosis at 33% compared to 7%. For radiation delivery specifically for primary brain tumors or metastases, brain tissue dose tolerance is the limiting factor when deciding on reirradiation. Incidence and severity of radiation necrosis seems to be both dose and volume dependent. When fraction doses are less than 2.5 Gy, an incidence of CRN of 5% and 10% is predicted to occur at BEDs of 120 Gy and 150 Gy, respectively.[20] For increased fraction sizes ≥ 2.5 Gy, the CRN incidence and severity becomes more unpredictable.[20] For comparison, our data showed median BEDs at about 120 Gy in the CRN patients (119.4 Gy) and less than 120 Gy (106.6 Gy) in non-CRN patients.

Because the incidence of sinonasal malignancies is low and the number of patients that develop CRN following radiation treatment for sinonasal malignancy is even smaller, there is inherent heterogeneity in radiation administration, tumor histology, and tumor location, making adequately powered statistical comparisons challenging. However, understanding that reirradiation is associated with an increased risk of CRN lends itself to additional avenues of study on the effect of alternate dose-fractionation schedules and timing of reirradiation.

5 | CONCLUSION

Reirradiation and tumor skull base involvement were significant risk factors associated with CRN in our study. Although a larger proportion of patients who developed CRN underwent high dose per fraction irradiation with CyberKnife SBRT as opposed to conventionally fractionated IMRT, this was not statistically significant. Higher average total and biologically effective radiation dosages of radiation were seen in the CRN groups, but these differences were not statistically significant. Gender, comorbidities, tumor subsite, and treatment type were not significantly different between groups. Further studies are needed to investigate the mechanism of injury that leads to CRN following radiation to elucidate potential areas of intervention for both prevention and treatment.

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CONFLICT OF INTEREST STATEMENT

None declared.

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